

PTO/PCT Rec'd 09 AUG 2002

PATENT #4.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Irina Caminschi, et al.

Serial No.: 10/070,982

Filed: March 8, 2002

For: DENDRITIC CELL MEMBRANE
PROTEIN FIRE

Group Art Unit: Unknown

Examiner: Unknown

Atty. Dkt. No.: FBRC:011US

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DATE OF DEPOSIT August 9, 2002

SECOND PRELIMINARY AMENDMENT**BOX PCT**

Commissioner for Patents
Washington, D.C. 20231

Sir:

Please amend the above-identified patent application as follows:

AMENDMENT**In the specification:**

Please insert as the first paragraph of the specification the following paragraph:

This is a U.S. National Application under 35 U.S.C. § 371 of International Application
No. PCT/AU00/01083 filed on September 11, 2000, which claims the benefit of priority to AU
PQ 2728 filed on September 9, 1999.

In the claims:

Please amend claim 1 as follows:

10/16/2002 SANDED1 00000006 10070982

01 FC:1615

486.00 OP

1. An isolated polypeptide comprising the amino acid sequence of SEQ ID NO:1 or a functional fragment thereof or an amino acid sequence having at least 50% identity to the amino acid sequence of SEQ ID NO:1 or a functional fragment thereof.

Please add the following new claims:

27. (New) The isolated polypeptide of claim 1, wherein the amino acid sequence has at least 50% identity to the amino acid sequence of SEQ ID NO: 1.
28. (New) The isolated polypeptide of claim 27, wherein the amino acid sequence has at least 70% identity to the amino acid sequence of SEQ ID NO: 1.
29. (New) The isolated polypeptide of claim 27, wherein the amino acid sequence has at least 80% identity to the amino acid sequence of SEQ ID NO: 1.
30. (New) The isolated polypeptide of claim 27, wherein the amino acid sequence has at least 90% identity to the amino acid sequence of SEQ ID NO: 1.
31. (New) An isolated polypeptide comprising the amino acid sequence of SEQ ID NO:2 or a functional fragment thereof or an amino acid sequence having at least 50% identity to the amino acid sequence of SEQ ID NO:2 or a functional fragment thereof.
32. (New) The isolated polypeptide of claim 31, wherein the amino acid sequence has at least 50% identity to the amino acid sequence of SEQ ID NO: 2.
33. (New) The isolated polypeptide of claim 32, wherein the amino acid sequence has at least 70% identity to the amino acid sequence of SEQ ID NO: 2.
34. (New) The isolated polypeptide of claim 32, wherein the amino acid sequence has at least 80% identity to the amino acid sequence of SEQ ID NO: 2.
35. (New) The isolated polypeptide of claim 32, wherein the amino acid sequence has at least 90% identity to the amino acid sequence of SEQ ID NO: 2.

36. (New) An isolated ligand, wherein the ligand interacts with a functional fragment of SEQ ID NO: 1 or SEQ ID NO: 2.
37. (New) The isolated ligand of claim 36, wherein the functional fragment has at least 50% identity to the amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 2.
38. (New) The isolated ligand of claim 36, wherein the functional fragment has at least 70% identity to the amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 2.
39. (New) The isolated ligand of claim 36, wherein the functional fragment has at least 80% identity to the amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 2.
40. (New) The isolated ligand of claim 36, wherein the functional fragment has at least 90% identity to the amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 2.
41. (New) The isolated ligand of claim 36, wherein the functional fragment has the amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 2.
42. (New) The isolated ligand of claim 36, wherein the ligand is an antibody.
43. (New) The isolated ligand of claim 42, wherein the ligand is the binding portion of the antibody.
44. (New) An isolated nucleic acid molecule comprising the sequence of SEQ ID NO:3, a sequence having at least 60% identity to the sequence of SEQ ID NO:3, a sequence which hybridizes to the sequence of SEQ ID NO:3 under stringent conditions, or a sequence encoding a functional analogue of a polypeptide of SEQ ID NO:1.
45. (New) The isolated nucleic acid molecule of claim 44, wherein the nucleic acid molecule comprises a sequence of at least 60% identity with the sequence of SEQ ID NO:3.
46. (New) The isolated nucleic acid molecule of claim 45, wherein the nucleic acid molecule comprises a sequence of at least 70% identity with the sequence of SEQ ID NO:3.
47. (New) The isolated nucleic acid molecule of claim 45, wherein the nucleic acid molecule comprises a sequence of at least 80% identity with the sequence of SEQ ID NO:3.

- 25146561.1

61. (New) The composition of claim 56, wherein the antigen is conjugated to the ligand.
62. (New) A composition for use in raising or lowering an immune response in a subject comprising a nucleic acid molecule and a carrier, wherein the nucleic acid molecule comprises a first sequence encoding a ligand that interacts with a functional fragment of SEQ ID NO: 1 or SEQ ID NO: 2 and a second sequence encoding an antigen.
63. (New) A method of screening a putative compound for immunological regulatory activity comprising;
 - (a) reacting the compound with a polypeptide comprising the amino acid sequence of SEQ ID NO:1 or a functional fragment thereof or an amino acid sequence having at least 50% identity to the amino acid sequence of SEQ ID NO:1 or a functional fragment thereof; and
 - (b) measuring the interaction between the compound and the polypeptide.
64. (New) A method of isolating an antigen presenting cell from a biological sample comprising contacting the biological sample with a ligand, wherein the ligand interacts with a functional fragment of SEQ ID NO: 1 or SEQ ID NO: 2, to form a complex between the ligand and the antigen presenting cell and isolating the complex formed between the ligand and the antigen presenting cell from the biological sample.
65. (New) The method of claim 64, wherein the ligand is immobilized on a solid support.
66. (New) A method of immunizing a subject comprising:
 - (a) isolating antigen presenting cells from a fluid sample obtained from the subject, wherein the isolation involves contacting the fluid sample with a ligand that interacts with a functional fragment of SEQ ID NO: 1 or SEQ ID NO: 2;
 - (b) exposing the cells isolated from step (a) to an antigen; and
 - (c) reintroducing the cells from step (b) into the subject.

67. (New) The method of claim 66, further comprising the step of growing the antigen presenting cells *in vitro* after step (a).
68. A method of immunizing a subject comprising:
 - (a) obtaining a fluid sample from the subject;
 - (b) isolating precursor cells from the fluid sample by contacting the fluid sample with a ligand that interacts with a functional fragment of SEQ ID NO: 1 or SEQ ID NO: 2;
 - (c) growing the cells isolated from step (a) *in vitro* such that they mature and differentiate to become antigen presenting cells;
 - (d) exposing the cells obtained in step (c) to an antigen; and
 - (e) reintroducing the cells from step (d) into the subject.
69. (New) A method of modulating an immune response in a subject comprising administering to the subject a ligand that interacts with a functional fragment of SEQ ID NO: 1 or SEQ ID NO: 2 such that the ligand binds to and inhibits the function of an antigen presenting cell.
70. (New) The method of claim 69, wherein the antigen presenting cell is a myeloid dendritic cell.
71. (New) The method of claim 69, further comprising the step of administering an antigen to the subject.
72. (New) The method of claim 71, wherein the antigen is administered after administration of the ligand.

REMARKS

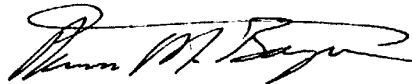
I. State of the claims

Claims 1-26 were present in the PCT application and were filed with the application on March 8, 2002. Claims 2-26 were cancelled without prejudice or disclaimer in a First Preliminary Amendment filed concurrently with the application. Applicants expressly reserved the right to pursue claims to the subject matter of claims 2-26. Applicants add by the present amendment claims 27-72. Therefore, claims 1 and 27-72 are currently pending. No new matter is introduced by these amendments.

II. Conclusion

Examination of the amended claims is respectfully requested.

Respectfully submitted,



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Date: August 9, 2002

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Express Mail Cert. No. EL794535315US
Date: March 8, 2002

PATENT

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
DO/EO/US RECEIVING OFFICE**

Applicants for DO/EO/US:

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VANDENABEELE, Mark Dexter WRIGHT,
Kenneth Douglas SHORTMAN

Atty. Dkt. No.: FBRC:011/TMB

International Application No.: PCT/AU00/01083

International Filing Date: 11 September 2000

Title: DENDRITIC CELL MEMBRANE PROTEIN
FIRE

PRELIMINARY AMENDMENT

BOX PCT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Please amend the above-identified patent application as follows:

AMENDMENT

In the claims:

Please cancel without prejudice or disclaimer claims 2-26.

REMARKS

I. State of the claims

Claims 1-26 were present in the PCT application and were filed herewith. Claims 2-26 have been cancelled without prejudice or disclaimer. Applicants expressly reserve the right to pursue claims to the subject matter of claims 2-26.

II. Conclusion

The claims have been amended to eliminate multiple dependencies. Examination of the amended claim is respectfully requested.

No fees are believed to be due in connection with the filing of this Preliminary Amendment; however, should any fees under 37 C.F.R §§ 1.16 to 1.21 be deemed necessary for any reason relating to the enclosed materials, the Commissioner is hereby authorized to deduct said fees from Fulbright & Jaworski Deposit Account No. 50-1212/10011874/TMB.

Respectfully submitted,



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Date: March 8, 2002

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<210> 5
 <211> 886
 <212> PRT
 <213> Homo sapiens

<400> 5
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 Ser Trp Glu Gly His Ile Arg Pro Thr Arg Lys Pro Asn Thr Lys Gly
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 Asn Asn Cys Arg Asp Ser Thr Leu Cys Pro Ala Tyr Ala Thr Cys Thr
 35 40 45
 Asn Thr Val Asp Ser Tyr Tyr Cys Thr Cys Lys Gln Gly Phe Leu Ser
 50 55 60
 Ser Asn Gly Gln Asn His Phe Lys Asp Pro Gly Val Arg Cys Lys Asp
 65 70 75 80
 Ile Asp Glu Cys Ser Gln Ser Pro Gln Pro Cys Gly Pro Asn Ser Ser
 85 90 95
 Cys Lys Asn Leu Ser Gly Arg Tyr Lys Cys Ser Cys Leu Asp Gly Phe
 100 105 110
 Ser Ser Pro Thr Gly Asn Asp Trp Val Pro Gly Lys Pro Gly Asn Phe
 115 120 125
 Ser Cys Thr Asp Ile Asn Glu Cys Leu Thr Ser Arg Val Cys Pro Glu
 130 135 140
 His Ser Asp Cys Val Asn Ser Met Gly Ser Tyr Ser Cys Ser Cys Gln
 145 150 155 160
 Val Gly Phe Ile Ser Arg Asn Ser Thr Cys Glu Asp Val Asn Glu Cys
 165 170 175
 Ala Asp Pro Arg Ala Cys Pro Glu His Ala Thr Cys Asn Asn Thr Val
 180 185 190
 Gly Asn Tyr Ser Cys Phe Cys Asn Pro Gly Phe Glu Ser Ser Ser Gly
 195 200 205
 His Leu Ser Cys Gln Gly Leu Lys Ala Ser Cys Glu Asp Ile Asp Glu
 210 215 220

Handwritten musical notation on a five-line staff.

LONGER

Ser Arg Val Val Gly Gly Ile Met Thr Gly Glu Lys Lys Asp Gly Phe
515 520 525

Ser Asp Pro Ile Ile Tyr Thr Leu Glu Asn Val Gln Pro Lys Gln Lys
530 535 540

Phe Glu Arg Pro Ile Cys Val Ser Trp Ser Thr Asp Val Lys Gly Gly
545 550 555 560

Arg Trp Thr Ser Phe Gly Cys Val Ile Leu Glu Ala Ser Glu Thr Tyr
565 570 575

Thr Ile Cys Ser Cys Asn Gln Met Ala Asn Leu Ala Val Ile Met Ala
580 585 590

Ser Gly Glu Leu Thr Met Asp Phe Ser Leu Tyr Ile Ile Ser His Val
595 600 605

Gly Ile Ile Ile Ser Leu Val Cys Leu Val Leu Ala Ile Ala Thr Phe
610 615 620

Leu Leu Cys Arg Ser Ile Arg Asn His Asn Thr Tyr Leu His Leu His
625 630 635 640

Leu Cys Val Cys Leu Leu Leu Ala Lys Thr Leu Phe Leu Ala Gly Ile
645 650 655

His Lys Thr Asp Asn Lys Thr Gly Cys Ala Ile Ile Ala Gly Phe Leu
660 665 670

His Tyr Leu Phe Leu Ala Cys Phe Phe Trp Met Leu Val Glu Ala Val
675 680 685

Ile Leu Phe Leu Met Val Arg Asn Leu Lys Val Val Asn Tyr Phe Ser
690 695 700

Ser Arg Asn Ile Lys Met Leu His Ile Cys Ala Phe Gly Tyr Gly Leu
705 710 715 720

Pro Met Leu Val Val Val Ile Ser Ala Ser Val Gln Pro Gln Gly Tyr
725 730 735

Gly Met His Asn Arg Cys Trp Leu Asn Thr Glu Thr Gly Phe Ile Trp
740 745 750

Ser Phe Leu Gly Pro Val Cys Thr Val Ile Val Ile Asn Ser Leu Leu
755 760 765

Leu Thr Trp Thr Leu Trp Ile Leu Arg Gln Arg Leu Ser Ser Val Asn
770 775 780

Ala Glu Val Ser Thr Leu Lys Asp Thr Arg Leu Leu Thr Phe Lys Ala
785 790 795 800

Phe Ala Gln Leu Phe Ile Leu Gly Cys Ser Trp Val Leu Gly Ile Phe

165										170					175				
Cys	Val	Thr	Arg	Asp	Val	Cys	Pro	Glu	His	Ala	Thr	Cys	His	Asn	Thr				
180										185					190				
Leu	Gly	Ser	Tyr	Tyr	Cys	Thr	Cys	Asn	Ser	Gly	Leu	Glu	Ser	Ser	Gly				
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Gly	Gly	Pro	Met	Phe	Gln	Gly	Leu	Asp	Glu	Ser	Cys	Glu	Asp	Val	Asp				
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Glu	Cys	Ser	Arg	Asn	Ser	Thr	Leu	Cys	Gly	Pro	Thr	Phe	Ile	Cys	Ile				
225										230					235				
Asn	Thr	Leu	Gly	Ser	Tyr	Ser	Cys	Ser	Cys	Pro	Ala	Gly	Phe	Ser	Leu				
245										250					255				
Pro	Thr	Phe	Gln	Ile	Leu	Gly	His	Pro	Ala	Asp	Gly	Asn	Cys	Thr	Asp				
260										265					270				
Ile	Asp	Glu	Cys	Asp	Asp	Thr	Cys	Pro	Leu	Asn	Ser	Ser	Cys	Thr	Asn				
275										280					285				
Thr	Ile	Gly	Ser	Tyr	Phe	Cys	Thr	Cys	His	Pro	Gly	Phe	Ala	Ser	Ser				
290										295					300				
Asn	Gly	Gln	Leu	Asn	Phe	Lys	Asp	Leu	Glu	Val	Thr	Cys	Glu	Asp	Ile				
305										310					315				
Asp	Glu	Cys	Thr	Gln	Asp	Pro	Leu	Gln	Cys	Gly	Leu	Asn	Ser	Val	Cys				
325										330					335				
Thr	Asn	Val	Pro	Gly	Ser	Tyr	Ile	Cys	Gly	Cys	Leu	Pro	Asp	Phe	Gln				
340										345					350				
Met	Asp	Pro	Glu	Gly	Ser	Gln	Gly	Tyr	Gly	Asn	Phe	Asn	Cys	Lys	Arg				
355										360					365				
Ile	Leu	Phe	Lys	Cys	Lys	Glu	Asp	Leu	Ile	Leu	Gln	Ser	Glu	Gln	Ile				
370										375					380				
Gln	Gln	Cys	Gln	Ala	Val	Gln	Gly	Arg	Asp	Leu	Gly	Tyr	Ala	Ser	Phe				
385										390					395				
Cys	Thr	Leu	Val	Asn	Ala	Thr	Phe	Thr	Ile	Leu	Asp	Asn	Thr	Cys	Glu				
405										410					415				
Asn	Lys	Ser	Ala	Pro	Val	Ser	Leu	Gln	Ser	Ala	Ala	Thr	Ser	Val	Ser				
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Leu	Val	Leu	Glu	Gln	Ala	Thr	Thr	Trp	Phe	Glu	Leu	Ser	Lys	Glu	Glu				
435										440					445				
Thr	Ser	Thr	Leu	Gly	Thr	Ile	Leu	Leu	Glu	Thr	Val	Glu	Ser	Thr	Met				
450										455					460				

Ile Lys Met Leu His Leu Cys Ala Phe Gly Tyr Gly Leu Pro Val Leu
755 760 765

Val Val Ile Ile Ser Ala Ser Val Gln Pro Arg Gly Tyr Gly Met His
770 775 780

Asn Arg Cys Trp Leu Asn Thr Glu Thr Gly Phe Ile Trp Ser Phe Leu
785 790 795 800

Gly Pro Val Cys Met Ile Ile Thr Ile Asn Ser Val Leu Leu Ala Trp
805 810 815

Thr Leu Trp Val Leu Arg Gln Lys Leu Cys Ser Val Ser Ser Glu Val
820 825 830

Ser Lys Leu Lys Asp Thr Arg Leu Leu Thr Phe Lys Ala Ile Ala Gln
835 840 845

Ile Phe Ile Leu Gly Cys Ser Trp Val Leu Gly Ile Phe Gln Ile Gly
850 855 860

Pro Leu Ala Ser Ile Met Ala Tyr Leu Phe Thr Ile Ile Asn Ser Leu
865 870 875 880

Gln Gly Ala Phe Ile Phe Leu Ile His Cys Leu Leu Asn Arg Gln Val
885 890 895

Arg Asp Glu Tyr Lys Lys Leu Leu Thr Arg Lys Thr Asp Leu Ser Ser
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Lys Met Gly
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35 40 45

Ser Ser Phe Ser Glu Ile Ile Thr Thr Pro Thr Glu Thr Cys Asp Asp
50 55 60

[illegible]

355	360	365
Phe Ala Phe Ser His Leu Glu Ser Ser Asp Gly Glu Ala Gly Arg Asp		
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Pro Pro Ala Lys Asp Val Met Pro Gly Pro Arg Gln Glu Leu Leu Cys		
385	390	395 400
Ala Phe Trp Lys Ser Asp Ser Asp Arg Gly Gly His Trp Ala Thr Glu		
	405	410 415
Val Cys Gln Val Leu Gly Ser Lys Asn Gly Ser Thr Thr Cys Gln Cys		
	420	425 430
Ser His Leu Ser Ser Phe Thr Ile Leu Met Ala His Tyr Asp Val Glu		
	435	440 445
Asp Trp Lys Leu Thr Leu Ile Thr Arg Val Gly Leu Ala Leu Ser Leu		
	450	455 460
Phe Cys Leu Leu Leu Cys Ile Leu Thr Phe Leu Leu Val Arg Pro Ile		
465	470	475 480
Gln Gly Ser Arg Thr Thr Ile His Leu His Leu Cys Ile Cys Leu Phe		
	485	490 495
Val Gly Ser Thr Ile Phe Leu Ala Gly Ile Glu Asn Glu Gly Gly Gln		
	500	505 510
Val Gly Leu Arg Cys Arg Leu Val Ala Gly Leu Leu His Tyr Cys Phe		
	515	520 525
Leu Ala Ala Phe Cys Trp Met Ser Leu Glu Gly Leu Glu Leu Tyr Phe		
	530	535 540
Leu Val Val Arg Val Phe Gln Gly Gln Gly Leu Ser Thr Arg Trp Leu		
545	550	555 560
Cys Leu Ile Gly Tyr Gly Val Pro Leu Leu Ile Val Gly Val Ser Ala		
	565	570 575
Ala Ile Tyr Ser Lys Gly Tyr Gly Arg Pro Arg Tyr Cys Trp Leu Asp		
	580	585 590
Phe Glu Gln Gly Phe Leu Trp Ser Phe Leu Gly Pro Val Thr Phe Ile		
	595	600 605
Ile Leu Cys Asn Ala Val Ile Phe Val Thr Thr Val Trp Lys Leu Thr		
	610	615 620
Gln Lys Phe Ser Glu Ile Asn Pro Asp Met Lys Lys Leu Lys Lys Ala		
625	630	635 640
Arg Ala Leu Thr Ile Thr Ala Ile Ala Gln Leu Phe Leu Leu Gly Cys		
	645	650 655

Thr Trp Val Phe Gly Leu Phe Ile Phe Asp Asp Arg Ser Leu Val Leu
 660 665 670

Thr Tyr Val Phe Thr Ile Leu Asn Cys Leu Gln Gly Ala Phe Leu Tyr
 675 680 685

Leu Leu His Cys Leu Leu Asn Lys Lys Val Arg Glu Glu Tyr Arg Lys
 690 695 700

Trp Ala Cys Leu Val Ala Gly Gly Ser Lys Tyr Ser Glu Phe Thr Ser
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Thr Thr Ser Gly Thr Gly His Asn Gln Thr Arg Ala Leu Arg Ala Ser
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Glu Ser Gly Ile
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<210> 8

<211> 30

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: PCR primers

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ctacggatcc aatatttcag cttcctgtcc

30

<210> 9

<211> 32

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: PCR primers

<400> 9

cgcgaagctt tcaatcttga catttctcat gg

32

<210> 10

<211> 34

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: PCR primers

<400> 10

gacgggatcc aatgagtgtc tactgaaaga attg

34

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<210> 11
<211> 34
<212> DNA
<213> Artificial Sequence
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<220>
<223> Description of Artificial Sequence: PCR primers

<400> 11
accggaagctt tcagctcttg ttcacataac aatc 34

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<210> 12
<211> 30
<212> DNA
<213> Artificial Sequence
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<220>
<223> Description of Artificial Sequence: PCR primers

<400> 12
ctacggatcc aatatttcag cttcctgtcc 30

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<210> 13
<211> 34
<212> DNA
<213> Artificial Sequence
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<220>
<223> Description of Artificial Sequence: PCR primers

<400> 13
accgaagctt tcagctcttg ttcacataac aatc 34

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<210> 14
<211> 31
<212> DNA
<213> Artificial Sequence
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<223> Description of Artificial Sequence: PCR primers

<400> 14
acacggatcc actttgggag tactgagtga a 31

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<210> 15
<211> 32
<212> DNA
<213> Artificial Sequence
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 $\langle 220 \rangle$

<223> Description of Artificial Sequence: PCR primers

<400> 15
cgctaagctt tcatagagcc atgagcacag ca 32

<210> 16
<211> 20
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<213> Mus musculus

<400> 16
cacctgcagc tcttccatct 20

<210> 17
<211> 23
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<213> Mus musculus

<400> 17
gaaagtttgc ttctcaaaat cca 23

<210> 18
<211> 26
<212> DNA
<213> Homo sapiens

<400> 18
tgtctcattg cacctcttgg tttcat 26

<210> 19
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<212> DNA
<213> Homo sapiens

<400> 19
ccacaacagc acccactgt 19

<210> 20
<211> 33
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: PCR primer

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tagtagacgc gtatattaca aatgatgaat att 33

<210> 21

<211> 33
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<223> Description of Artificial Sequence: PCR primer

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<210> 22
<211> 26
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<210> 23
<211> 33
<212> DNA
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<220>
<223> Description of Artificial Sequence: PCR primer

<400> 23
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<210> 24
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<220>
<223> Description of Artificial Sequence: PCR primer

<400> 24
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<210> 25
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<223> Description of Artificial Sequence: PCR primer

<400> 25

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SEQUENCE LISTING

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<130> FBRC:011US

<140> 10/070,982

<141> 2002-03-08

<150> PCT/AU00/01083

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<211> 681

<212> PRT

<213> Mus musculus

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			20					25					30		

Cys	Asn	Glu	Asn	Ala	Ser	Cys	Phe	Asn	Ser	Thr	His	Cys	Val	Cys	Lys
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Glu	Gly	Phe	Trp	Thr	Gly	Ser	Glu	Asn	Arg	Arg	Ile	Ile	Glu	Pro	His
	50					55					60				

Glu	Lys	Cys	Gln	Asp	Ile	Asn	Glu	Cys	Leu	Leu	Lys	Glu	Leu	Val	Cys
65					70					75					80

Lys	Asp	Val	Ser	Tyr	Cys	Arg	Asn	Lys	Ile	Gly	Thr	Tyr	Ile	Cys	Ser
				85					90					95	

Cys	Val	Val	Lys	Tyr	Pro	Leu	Phe	Asn	Trp	Val	Ala	Gly	Ile	Ile	Asn
			100					105					110		

Ile	Asp	His	Pro	Asp	Cys	Tyr	Val	Asn	Lys	Ser	Lys	Asn	Thr	Gly	Ser
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Lys	Thr	His	Thr	Leu	Gly	Val	Leu	Ser	Glu	Phe	Lys	Ser	Lys	Glu	Glu
	130					135					140				

Val	Ala	Lys	Gly	Ala	Thr	Lys	Leu	Leu	Arg	Lys	Val	Glu	His	His	Ile
145					150					155					160

Leu	Asn	Glu	Asn	Ser	Asp	Ile	Pro	Lys	Lys	Asp	Glu	Asn	Pro	Leu	Leu
				165					170					175	

$$\frac{1}{n} \sum_{i=1}^n \left(\frac{\partial}{\partial \theta} \log f(\mathbf{x}_i; \theta) \right)^T = 0$$

Ser Leu His Arg Gly Phe Ile Trp Ser Phe Leu Gly Pro Ala Ala Ala
485 490 495

Ile Ile Leu Ile Asn Leu Val Phe Tyr Phe Leu Ile Ile Trp Ile Leu
500 505 510

Arg Ser Lys Leu Ser Ser Leu Asn Lys Glu Val Ser Thr Leu Gln Asp
515 520 525

Thr Lys Val Met Thr Phe Lys Ala Ile Val Gln Leu Phe Val Leu Gly
530 535 540

Cys Ser Trp Gly Ile Gly Leu Phe Ile Phe Ile Glu Val Gly Lys Thr
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Val Arg Leu Ile Val Ala Tyr Leu Phe Thr Ile Ile Asn Val Leu Gln
565 570 575

Gly Val Leu Ile Phe Met Val His Cys Leu Leu Asn Arg Gln Val Arg
580 585 590

Met Glu Tyr Lys Lys Trp Phe His Arg Leu Arg Lys Glu Val Glu Ser
595 600 605

Glu Ser Thr Glu Val Ser His Ser Thr Thr His Thr Lys Met Gly Leu
610 615 620

Ser Leu Asn Leu Glu Asn Phe Cys Pro Thr Gly Asn Leu His Asp Pro
625 630 635 640

Ser Asp Ser Ile Leu Pro Ser Thr Glu Val Ala Gly Val Tyr Leu Ser
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Ala Tyr Trp Ser Arg Thr Ile Ser Asp
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<210> 2
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Phe His Asp Ser Ser Glu Lys Cys Glu Asp Ile Asn Glu Cys Glu Thr
35 40 45

Gly Leu Ala Lys Cys Lys Tyr Lys Ala Tyr Cys Arg Asn Lys Val Gly
50 55 60

[illegible]

Pro Glu Val Leu Cys Ser Ile Ile Ala Gly Leu Leu His Phe Leu Tyr
370 375 380

Leu Ala Cys Phe Thr Trp Met Leu Leu Glu Gly Leu His Leu Phe Leu
385 390 395 400

Thr Val Arg Asn Leu Lys Val Ala Asn Tyr Thr Ser Thr Gly Arg Phe
405 410 415

Lys Lys Arg Phe Met Tyr Pro Val Gly Tyr Gly Ile Pro Ala Val Ile
420 425 430

Ile Ala Val Ser Ala Ile Val Gly Pro Gln Asn Tyr Gly Thr Phe Thr
435 440 445

His Cys Trp Leu Lys Leu Asp Lys Gly Phe Ile Trp Ser Phe Met Gly
450 455 460

Pro Val Ala Val Ile Ile Leu Ile Asn Leu Val Phe Tyr Phe Gln Val
465 470 475 480

Leu Trp Ile Leu Arg Ser Lys Leu Ser Ser Leu Asn Lys Glu Val Ser
485 490 495

Thr Ile Gln Asp Thr Arg Val Met Thr Phe Lys Ala Ile Ser Gln Leu
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Phe Ile Leu Gly Cys Ser Trp Gly Leu Gly Phe Phe Met Val Glu Glu
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Val Gly Lys Thr Ile Gly Ser Ile Ile Ala Tyr Ser Phe Thr Ile Ile
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Asn Thr Leu Gln Gly Val Leu Leu Phe Val Val His Cys Leu Leu Asn
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565 570 575

Gly Val Glu Thr Glu Ser Thr Glu Met Ser Arg Ser Thr Thr Gln Thr
580 585 590

Lys Thr Glu Glu Val Gly Lys Ser Ser Glu Ile Phe His Lys Gly Gly
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610 615 620

His Leu Val Ser Ala Ala Trp Leu Lys Met Asn
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<213> Mus musculus

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<210> 4
 <211> 2798
 <212> DNA
 <213> Homo sapiens

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 gaagatatta atgaatgtga aaccgggctg gcaaagtgc agtataaagc atattgtagg 180
 aataaagttg gaggttacat ctgtagctgt ttggtaaaat atactttatt caactttctg 240
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 tctccaggaa aggggtcaaat ttctgaattt gatatagtct atgaaaccaa gaggtgcaat 480
 gagacaaggg agaattgcttt tctggaagct ggaaataaca ccatggatat caactgtgct 540
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<210> 5

<211> 886

<212> PRT

<213> Homo sapiens

<400> 5

Met Arg Gly Phe Asn Leu Leu Leu Phe Trp Gly Cys Cys Val Met His
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Ser Trp Glu Gly His Ile Arg Pro Thr Arg Lys Pro Asn Thr Lys Gly
20 25 30

Asn Asn Cys Arg Asp Ser Thr Leu Cys Pro Ala Tyr Ala Thr Cys Thr
35 40 45

Asn Thr Val Asp Ser Tyr Tyr Cys Thr Cys Lys Gln Gly Phe Leu Ser
50 55 60

Ser Asn Gly Gln Asn His Phe Lys Asp Pro Gly Val Arg Cys Lys Asp
65 70 75 80

Ile Asp Glu Cys Ser Gln Ser Pro Gln Pro Cys Gly Pro Asn Ser Ser
85 90 95

Cys Lys Asn Leu Ser Gly Arg Tyr Lys Cys Ser Cys Leu Asp Gly Phe
100 105 110

Ser Ser Pro Thr Gly Asn Asp Trp Val Pro Gly Lys Pro Gly Asn Phe
115 120 125

Ser Cys Thr Asp Ile Asn Glu Cys Leu Thr Ser Arg Val Cys Pro Glu
130 135 140

His Ser Asp Cys Val Asn Ser Met Gly Ser Tyr Ser Cys Ser Cys Gln
145 150 155 160

Val Gly Phe Ile Ser Arg Asn Ser Thr Cys Glu Asp Val Asn Glu Cys
165 170 175

Ala Asp Pro Arg Ala Cys Pro Glu His Ala Thr Cys Asn Asn Thr Val
180 185 190

Gly Asn Tyr Ser Cys Phe Cys Asn Pro Gly Phe Glu Ser Ser Ser Gly
195 200 205

His Leu Ser Cys Gln Gly Leu Lys Ala Ser Cys Glu Asp Ile Asp Glu
210 215 220

Cys Thr Glu Met Cys Pro Ile Asn Ser Thr Cys Thr Asn Thr Pro Gly
225 230 235 240

Ser Tyr Phe Cys Thr Cys His Pro Gly Phe Ala Pro Ser Ser Gly Gln
245 250 255

Leu Asn Phe Thr Asp Gln Gly Val Glu Cys Arg Asp Ile Asp Glu Cys
260 265 270

Arg Gln Asp Pro Ser Thr Cys Gly Pro Asn Ser Ile Cys Thr Asn Ala

275	280	285
Leu Gly Ser Tyr Ser Cys Gly Cys Ile Val Gly Phe His Pro Asn Pro		
290	295	300
Glu Gly Ser Gln Lys Asp Gly Asn Phe Ser Cys Gln Arg Val Leu Phe		
305	310	315 320
Lys Cys Lys Glu Asp Val Ile Pro Asp Asn Lys Gln Ile Gln Gln Cys		
	325	330 335
Gln Glu Gly Thr Ala Val Lys Pro Ala Tyr Val Ser Phe Cys Ala Gln		
	340	345 350
Ile Asn Asn Ile Phe Ser Val Leu Asp Lys Val Cys Glu Asn Lys Thr		
	355	360 365
Thr Val Val Ser Leu Lys Asn Thr Thr Glu Ser Phe Val Pro Val Leu		
	370	375 380
Lys Gln Ile Ser Met Trp Thr Lys Phe Thr Lys Glu Glu Thr Ser Ser		
385	390	395 400
Leu Ala Thr Val Phe Leu Glu Ser Val Glu Ser Met Thr Leu Ala Ser		
	405	410 415
Phe Trp Lys Pro Ser Ala Asn Val Thr Pro Ala Val Arg Ala Glu Tyr		
	420	425 430
Leu Asp Ile Glu Ser Lys Val Ile Asn Lys Glu Cys Ser Glu Glu Asn		
	435	440 445
Val Thr Leu Asp Leu Val Ala Lys Gly Asp Lys Met Lys Ile Gly Cys		
	450	455 460
Ser Thr Ile Glu Glu Ser Glu Ser Thr Glu Thr Thr Gly Val Ala Phe		
465	470	475 480
Val Ser Phe Val Gly Met Glu Ser Val Leu Asn Glu Arg Phe Phe Gln		
	485	490 495
Asp His Gln Ala Pro Leu Thr Thr Ser Glu Ile Lys Leu Lys Met Asn		
	500	505 510
Ser Arg Val Val Gly Gly Ile Met Thr Gly Glu Lys Lys Asp Gly Phe		
	515	520 525
Ser Asp Pro Ile Ile Tyr Thr Leu Glu Asn Val Gln Pro Lys Gln Lys		
	530	535 540
Phe Glu Arg Pro Ile Cys Val Ser Trp Ser Thr Asp Val Lys Gly Gly		
545	550	555 560
Arg Trp Thr Ser Phe Gly Cys Val Ile Leu Glu Ala Ser Glu Thr Tyr		
	565	570 575
Thr Ile Cys Ser Cys Asn Gln Met Ala Asn Leu Ala Val Ile Met Ala		

[illegible]

Val Gly Gly Thr Val Thr Gly Glu Lys Lys Glu Asp Phe Ser Lys Pro
 565 570 575
 Ile Ile Tyr Thr Leu Gln His Ile Gln Pro Lys Gln Lys Ser Glu Arg
 580 585 590
 Pro Ile Cys Val Ser Trp Asn Thr Asp Val Glu Asp Gly Arg Trp Thr
 595 600 605
 Pro Ser Gly Cys Glu Ile Val Glu Ala Ser Glu Thr His Thr Val Cys
 610 615 620
 Ser Cys Asn Arg Met Ala Asn Leu Ala Ile Ile Met Ala Ser Gly Glu
 625 630 635 640
 Leu Thr Met Glu Phe Ser Leu Tyr Ile Ile Ser His Val Gly Thr Val
 645 650 655
 Ile Ser Leu Val Cys Leu Ala Leu Ala Ile Ala Thr Phe Leu Leu Cys
 660 665 670
 Arg Ala Val Gln Asn His Asn Thr Tyr Met His Leu His Leu Cys Val
 675 680 685
 Cys Leu Phe Leu Ala Lys Ile Leu Phe Leu Thr Gly Ile Asp Lys Thr
 690 695 700
 Asp Asn Gln Thr Ala Cys Ala Ile Ile Ala Gly Phe Leu His Tyr Leu
 705 710 715 720
 Phe Leu Ala Cys Phe Phe Trp Met Leu Val Glu Ala Val Met Leu Phe
 725 730 735
 Leu Met Val Arg Asn Leu Lys Val Val Asn Tyr Phe Ser Ser Arg Asn
 740 745 750
 Ile Lys Met Leu His Leu Cys Ala Phe Gly Tyr Gly Leu Pro Val Leu
 755 760 765
 Val Val Ile Ile Ser Ala Ser Val Gln Pro Arg Gly Tyr Gly Met His
 770 775 780
 Asn Arg Cys Trp Leu Asn Thr Glu Thr Gly Phe Ile Trp Ser Phe Leu
 785 790 795 800
 Gly Pro Val Cys Met Ile Ile Thr Ile Asn Ser Val Leu Leu Ala Trp
 805 810 815
 Thr Leu Trp Val Leu Arg Gln Lys Leu Cys Ser Val Ser Ser Glu Val
 820 825 830
 Ser Lys Leu Lys Asp Thr Arg Leu Leu Thr Phe Lys Ala Ile Ala Gln
 835 840 845
 Ile Phe Ile Leu Gly Cys Ser Trp Val Leu Gly Ile Phe Gln Ile Gly
 850 855 860

[illegible]

Gln Gly Ala Phe Ile Phe Leu Ile His Cys Leu Leu Asn Arg Gln Val
885 890 895

Arg Asp Glu Tyr Lys Lys Leu Leu Thr Arg Lys Thr Asp Leu Ser Ser
900 905 910

His Ser Gln Thr Ser Gly Ile Leu Leu Ser Ser Met Pro Ser Thr Ser
915 920 925

Lys Met Gly
930

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<210> 7
<211> 740
<212> PRT
<213> Homo sapiens
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<400> 7
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Gly Ala Glu Thr Gln Asp Ser Arg Gly Cys Ala Arg Val Cys Pro Gln
20 25 30

Asn Ser Ser Cys Val Asn Ala Thr Ala Cys Arg Cys Asn Pro Gly Phe
35 40 45

Ser Ser Phe Ser Glu Ile Ile Thr Thr Pro Thr Glu Thr Cys Asp Asp
50 55 60

Ile Asn Glu Cys Ala Thr Pro Ser Lys Val Ser Cys Gly Lys Phe Ser
65 70 75 80

Asp Cys Trp Asn Thr Glu Gly Ser Tyr Asp Cys Val Cys Ser Pro Gly
85 90 95

Tyr Glu Pro Val Ser Gly Ala Lys Thr Phe Lys Asn Glu Ser Glu Asn
100 105 110

Thr Cys Gln Asp Glu Cys Ser Ser Gly Gln His Gln Cys Asp Ser Ser
115 120 125

Thr	Val	Cys	Phe	Asn	Thr	Val	Gly	Ser	Tyr	Ser	Cys	Arg	Cys	Arg	Pro
130						135					140				

Gly	Trp	Lys	Pro	Arg	His	Gly	Ile	Pro	Asn	Asn	Gln	Lys	Asp	Thr	Val
145					150					155					160

Cys Glu Asp Met Thr Phe Ser Thr Trp Thr Pro Pro Pro Gly Val His
165 170 175

Ser Gln Thr Leu Ser Arg Phe Phe Asp Lys Val Gln Asp Leu Gly Arg
180 185 190

1991/1992, 1992/1993

Val Gly Ser Thr Ile Phe Leu Ala Gly Ile Glu Asn Glu Gly Gly Gln
500 505 510

Val Gly Leu Arg Cys Arg Leu Val Ala Gly Leu Leu His Tyr Cys Phe
515 520 525

Leu Ala Ala Phe Cys Trp Met Ser Leu Glu Gly Leu Glu Leu Tyr Phe
530 535 540

Leu Val Val Arg Val Phe Gln Gly Gln Gly Leu Ser Thr Arg Trp Leu
545 550 555 560

Cys Leu Ile Gly Tyr Gly Val Pro Leu Leu Ile Val Gly Val Ser Ala
565 570 575

Ala Ile Tyr Ser Lys Gly Tyr Gly Arg Pro Arg Tyr Cys Trp Leu Asp
580 585 590

Phe Glu Gln Gly Phe Leu Trp Ser Phe Leu Gly Pro Val Thr Phe Ile
595 600 605

Ile Leu Cys Asn Ala Val Ile Phe Val Thr Thr Val Trp Lys Leu Thr
610 615 620

Gln Lys Phe Ser Glu Ile Asn Pro Asp Met Lys Lys Leu Lys Lys Ala
625 630 635 640

Arg Ala Leu Thr Ile Thr Ala Ile Ala Gln Leu Phe Leu Leu Gly Cys
645 650 655

Thr Trp Val Phe Gly Leu Phe Ile Phe Asp Asp Arg Ser Leu Val Leu
660 665 670

Thr Tyr Val Phe Thr Ile Leu Asn Cys Leu Gln Gly Ala Phe Leu Tyr
675 680 685

Leu Leu His Cys Leu Leu Asn Lys Lys Val Arg Glu Glu Tyr Arg Lys
690 695 700

Trp Ala Cys Leu Val Ala Gly Gly Ser Lys Tyr Ser Glu Phe Thr Ser
705 710 715 720

Thr Thr Ser Gly Thr Gly His Asn Gln Thr Arg Ala Leu Arg Ala Ser
725 730 735

Glu Ser Gly Ile
740

<210> 8
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: PCR primers

<400> 8
ctacggatcc aatatttcag cttcctgtcc 30

<210> 9
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: PCR primers

<400> 9
cgcaagctt tcaatcttga catttctcat gg 32

<210> 10
<211> 34
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: PCR primers

<400> 10
gacgggatcc aatgagtgtc tactgaaaga attg 34

<210> 11
<211> 34
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: PCR primers

<400> 11
accgaagctt tcagctcttg ttcacataac aatc 34

<210> 12
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: PCR primers

<400> 12
ctacggatcc aatatttcag cttcctgtcc 30

<210> 13
<211> 34
<212> DNA
<213> Artificial Sequence

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<220>
<223> Description of Artificial Sequence: PCR primers

<400> 13
accgaagctt tcagctcttg ttcacataac aatc
34
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<210> 14
<211> 31
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: PCR primers

<400> 14
acacggatcc actttgggag .tactgagtga a
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<210> 15
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: PCR primers

<400> 15
cgctaagctt tcatagagcc atgagcacag ca
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<210> 16
<211> 20
<212> DNA
<213> Mus musculus

<400> 16
cacctgcagc tcttccatct 20
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<210> 17
<211> 23
<212> DNA
<213> Mus musculus

<400> 17
gaaagtgtttgc ttctcaaaat cca
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<210> 18
<211> 26
<212> DNA
<213> Homo sapiens

<400> 18
tgatctcattg cacctcttgg tttcat
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<210> 19
<211> 19
<212> DNA
<213> Homo sapiens

<400> 19
ccacaacagc acccactgt

19

<210> 20
<211> 33
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: PCR primer

<400> 20
tagtagacgc gtatattaca aatgatgaat att

33

<210> 21
<211> 33
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: PCR primer

<400> 21
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33

<210> 22
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: PCR primer

<400> 22
cgggatcctc ctcacggggg agagcc

26

<210> 23
<211> 33
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: PCR primer

<400> 23
cggggtaccac catgggaagc aggtgccttc tgc

33

